Amendments to the Drawings

Please delete Tables 3 and 4 (pages 226-227).

Please add Figures 2, 3, and 4 provided herewith.

Remarks

By the present communication, claims 1, 2, 7, 8, 12, 14, 16, 55, 66, 72, 74, 75, 78-81, 83, and 92 have been amended, claims 3, 4, 67-71, and 96 have been canceled and new claims 99-104 have been added. No new matter is introduced as the claimed subject matter is fully supported by the specification and claims as originally filed. In view of the amendments submitted herewith, claims 1, 2, 5-66, 72-95 and 97-104 are pending, with claims 1, 2, 5-16, 55, 66, 72-87, 92-95, and 97-104 under active prosecution. Amendments submitted herewith are not to be construed as a dedication of the subject matter not presently claimed to the public. Applicants reserve the right to pursue claims as originally filed in a continuation application. The Listing of Claims with appropriate status identifier begins on page 7 of this communication.

The specification is amended in paragraph **[0019]**, changing the patent number 8,837,815 to 5,837,815, which is the correctly referenced patent, entitled "PYK2 related polypeptide products". Paragraph **[0051]** is amended to provide the original paragraph as filed. Applicants note that in the Response to Notice to File Missing Parts filed on July 28, 2004, paragraph **[0051]** was mistakenly indicated as the paragraph being amended, when in fact, this should have been an amendment to paragraph **[0151]**. Paragraphs **[0146.1]** – **[0146.3]** are added to provide the descriptions of Figures 2-4, formerly the illustration on page 98 (contained within paragraph **[0366]**), Table 3, and Table 4, respectively. Paragraphs **[0148]** and **[0150]** are amended to insert the appropriate SEQ ID NO: for the PYK2 kinase domain. Paragraphs **[0151]** and **[0152]** are deleted as these Tables are now Figures 3 and 4, added in paragraphs **[0146.2]** and **[0146.3]**. Reference within the specification as originally filed to "Table 5" (i.e., at paragraphs **[0153]** and **[0392]**, and at page 231 in the table legend) has been updated to refer to Table 3, original Tables 3-4 having been presented as Figures 3-4, respectively. Paragraph **[0366]** is amended to insert the SEQ ID NO: for PYK2 residues 420-691. Further, the sequence shown (SEQ ID NO:7) is deleted and replaced by Figure 2, with the reference to Figure 2 added to the paragraph accordingly. Paragraph **[0376]** is amended to correct errors in the font used. The squares in the row for Unit Cell are replaced with β, while the square in the parameter listed between

Completeness and Rsym is replace with σ, to provide I/σ. These terms are well known to one of skill in the art of crystallography. Paragraphs **[0391]** and **[0392]** are amended to insert the appropriate SEQ ID NOS: after $(E4Y)_3$ and PYK2 kinase domain residues 419-691, respectively.

Claim 1 is amended to define the invention with greater particularity. The preamble language "identifying compounds binding to PYK2" is changed to "developing a ligand to PYK2", which finds support, for example, in specification paragraph **[0028]**. The fourth line is amended from "co-crystals" to "a co-crystal", which finds support, for example, in specification paragraph **[0094]**. Additional steps are added in lines 5-10, where modifying the structure of the compound and testing and identifying ligands with improved PYK2 binding or activity finds support, for example, in specification paragraph **[0028]**, with additional support for testing PYK2 binding or kinase activity provided, for example, in specification paragraphs **[0315]** – **[0321]** and **[0386]** – **[0392]**.

Claim 2 is amended to read "at least one compound", consistent with claim 1. Further, "binds weakly" is replaced with "binds with low or very low affinity", which finds support, for example, in specification paragraph **[0028]**.

Claim 7 is amended to be dependent from claim 1, as claim 4 has been canceled, and to include Formula I as the chemical structure, as supported, for example, in specification paragraphs **[0096]-[0105]**.

Claim 8 is amended to include lines 5-6, modifying a chemical structure to provide a derivative, as supported, for example, in specification paragraph **[0042]** and further in **[0052]**.

Claim 12 is amended to a method of developing "a ligand" in place of "ligands" specific for PYK2. The claim is also amended similarly to claim 8 to include the step of modifying a chemical structure of a compound, and line 5 is amended to include identification of a derivative with greater specificity as the ligand. These amendments find support in specification paragraphs **[0028]**, **[0042]**, and **[0052]**.

Claim 14 is amended to delete the inadvertent repetition of the term "residues" therefrom.

Claim 16 is amended similarly to claim 2, where "binds weakly" is replaced with "binds with low or very low affinity", which finds support, for example, in specification paragraph **[0028]**.

Claim 55 is amended to "a method of developing a ligand" rather than "a method of identifying a ligand". Further, lines 3-4 are added to modifying a chemical structure of a parent compound to provide a derivative that includes a core structure of Formula I, and the corresponding language in line 4, "a derivative compound that includes a core structure of Formula I" is amended to delete reference to Formula I, as this is included in added lines 3-4. The term "altered" is changed to "greater", and additional language is added identifying a derivative with greater affinity or specificity as a ligand. These amendments find support, for example, in specification paragraphs **[0028]**, and **[0042]**.

Claim 66 is amended in order to define the invention with greater particularity. The one-substructure is amended to be selected from an epitope, a mutation site, or an attachment point, and a step is added to forming the biological agent, where the agent is selected from an antibody or a modified PYK2. These amendments are supported by claims 67-71 as originally filed as well as, for example, the specification paragraphs **[0308]-[0314]**.

Claim 72 is amended to indicate that the compound fitted in an electronic representation is a compound of Formula I, which finds support, for example, in specification paragraph **[0079]**. The claim is also amended to include the step of identifying potential binding compounds based on their fit in the electronic representation. Support for this amendment is found, for example, in claims 74 and 75 as originally filed.

Claims 74 and 75 are amended to remove the step of identifying potential binding compounds based on their fit in the electronic representation, consistent with addition of this language to the parent claim 72.

Claim 78 is amended to correctly depend on claim 72, and to correct a language error, deleting the term "a" before "said compound".

Claim 79 is amended to define the invention with greater particularity. Lines 1-2 are amended to include "on the PYK2 binding compound" following energetically allowed sites, which finds support, for example, in specification paragraphs **[0089]** and **[0294]**, which discuss the attachment site or energetically allowed site on the PYK2 binding compound. The term "on a kinase binding compound" is deleted. This term is not necessary, as it is clear that the attachment component is attached to the kinase (i.e. PYK2) binding compound.

Claim 80 is amended to correct language errors, changing "a" to "said", correcting the spelling of attachment, and adding "thereof" after the term derivative, consistent with claim 79.

Claim 81 and 83 are amended to change "kinase" to "PYK2", consistent with claim 79.

Claim 92 is amended to include the steps of creating a homology model from PYK2 and including a compound of Formula I in the homology model, supported, for example, in specification paragraphs **[0057]-[0058]**, discussing use of homology models, and **[0079]**, discussing including a compound of Formula I in the binding site. Also, the inadvertent repetition of the term "residues" is deleted, the term "a compound of Formula I" is amended to read "the compound", as this term was added in line 5, and "of Formula I" is not necessary. The term "one or more" is added before residues in line 7, consistent with the language in line 2.

New claim 99 finds support, for example, in paragraphs **[0065]** and **[0373]**, where use of crystallization screening kits to identify crystallization conditions is described.

New claim 101 finds support, for example, in paragraph **[0064]**, describing the crystallization conditions.

New claim 103 finds support, for example, in paragraph **[0029]**, describing the PYK2 kinase domain as having at least 50 amino acid residues in length with greater than 90% amino acid sequence identity to at least a portion of SEQ ID NO: 1.

New claims 100, 102, and 104 find support, for example, in paragraphs **[0171] – [0191]**, describing the use of X-ray crystallography to determine crystal structure.

Applicants request entry of the foregoing amendments. In view of the preceding amendments and the remarks made herein, the present application is believed to be in condition for allowance.

Objections to the disclosure

The disclosure is objected to because of a number of informalities as follows:

(a) The illustration at page 98, and Tables 3 and 4 should be presented as Figures. Also, the Office Action indicates Table 4 is of low quality and too small. Applicants believe that this was intended to refer to Table 3. The illustration on page 98 and Tables 3 and 4 have been amended to be presented as Figures, with Table 3, now Figure 3, being amended to improve the quality of the Figure.

(b) The substrate biotin-(E4Y)3 at page 105 is not defined and requires a sequence identification number. The substrate is biotin-Glu-Glu-Glu-Glu-Tyr-Glu-Glu-Glu-Glu-Tyr-Glu-Glu-Glu-Glu-Tyr, for which the sequence identity number has been added.

(c) The parameters of Table 5 are not defined. As noted by the Examiner, Vmax has a well-established meaning in the art. Applicants believe that the other terms are also well established in the art, where K is the EC50 as determined by the curve fitting algorithm of MDL® Assay Explorer version 2,2,1,137 MDL (MDL® Information Systems, Inc., San Leandro, CA). The terms Vmax(SE) and K(SE) are simply the standard error in the measurements of

Vmax and K. K(lo 95%) and K(up 95%) are the low and high values of K at 95% confidence level, respectively.

(d) The table at page 101 has a square in one of the variables for unit cell dimension, which should be β. This has been corrected by amendment of the table in paragraph **[0376]**. This table is also amended to change I/square to correctly denote I/σ.

(e) The patent 8,837,815 has not yet issued. This inadvertent typographical error has been corrected by amendment of the patent number to 5,837,815, which is clearly the intended patent based on its title and content.

Further, the application contains sequence disclosures that are allegedly not identified with sequence identification numbers. The Office Action indicates that the following disclosures require appropriate sequence identification numbers:

Table 4, comprising disclosure of 14 amino acid sequences. Applicants believe that this was intended to reference Table 3. Applicants point out that in the Response to Notice to File Missing Parts that was filed on July 28, 2004, Applicants had attempted to correct this, but referenced paragraph **[0051]** rather than the paragraph **[0151]** that included the description of Table 3. The contents of Table 3 are presented herewith as Figure 3, for which the added description (paragraph **[0146.2]** includes the appropriate sequence identification number.

The phrase "biotin-(E4Y)3" in paragraph **[0391]** line 5, the sequence of paragraph **[0366]**, line 1, and the atomic coordinates of the sequence represented in Tables 1 and 2 are also asserted to require sequence identifiers. Applicants have amended paragraphs **[0148]**, **[0150]**, **[0366]**, and **[0391]**, to include the appropriate sequence identification number.

Rejection under 35 U.S.C. § 112, first paragraph (written description)

Claims 1-16, 55, 66-72, 78-87 and 92-98, although not explicitly stated in the Office Action, appear to be rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Office Action indicates the following on pages 5-6

> Claims...are directed to a method utilizing a co-crystal with any chemical entity or any crystal structure obtained from all possible crystals of any protein named PYK2, and its fragments and mutants from any biological source in identifying compounds that bind and inhibit any activity of PYK2. The specification, however, only provides the description of the polypeptide of, SEQ ID NO: 1...that produces a monocyclic crystal in space group $P2_1$, with cell unit dimension of...Also, the specification teach a crystal of PYK2 bound to the well known kinase inhibitor AMPPNP...but there is no description of the method of obtaining the co-crystal. There is no disclosure of any particular relationship between the amino acid sequences of SYK2 [sic] proteins the crystallization conditions as well as the structure of the inhibitors and the polypeptide and the crystallization conditions.

The Office Action continues with an analysis of the written description requirement, alleging that neither the applicants nor the prior art describe a crystal or crystallization of the full-length PYK2, and that the specification allegedly fails to describe additional representative species. The Office Action further alleges that Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

Applicants respectfully disagree with this rejection. Applicants summarize the invention of, for example, claim 1, as currently amended, directed to the development of a ligand to PYK2. The invention uses a co-crystal of PYK2 with a compound in determining the orientation of the compound within PYK2. Such a co-crystal is, therefore, a precondition to carrying out the claimed method. If no such co-crystal exists, one would not apply the invention method. If, on the other hand, such a co-crystal were available, one of skill in the art could readily carry out the invention method. A chemical structure of the compound is then modified to provide a potential ligand, which is then tested for activity against PYK2, such that those potential ligands with

either higher activity against PYK2 or binding to PYK2 with greater affinity or specificity, or both relative to the compound are identified as ligands.

Independent claims 8, 12 and 55 provide similar method steps. Claim 66 provides a method of developing a biological agent, where PYK2 crystal structure is analyzed, a sub-structure identified, and formation of the agent from the sub-structure. Claims 72 and 92 provide methods for developing a ligand or identifying potential PYK2 binding compounds using an electronic representation of a compound in a PYK2 binding site and identifying compounds that fit the site. Such methods are applicable to any co-crystal that may be formed from a suitable compound and PYK2 sequence, whether full-length or partial, or any crystal structures or electronic representations of PYK2 structures.

Applicants respectfully disagree with the Office Action statement that there is no description of the method of obtaining co-crystals. There is adequate description of both general and specific methods of obtaining co-crystals, for example in paragraphs **[0064]-[0065]**. In general, screening kits may be used to determine appropriate crystallization conditions, which could be applied by one of skill in the art to a variety of PYK2 sequences and compounds. Applicants have exemplified how to make and use one such crystal, and the description of how to use the data from such a crystal is sufficient to show Applicants were in possession of the claimed invention. Contrary to the suggestion in the Office Action, the invention is not directed to any co-crystal of any compound with any PYK2 related protein, rather it is directed to the use of information from such a crystal, where one such crystal is provided by example. Regarding claim 79, this claim does not include PYK2 co-crystals or electronic representations, but is directed to PYK2 binding compounds. Applicants respectfully request withdrawal of the 35 U.S.C. 112, first paragraph written description rejection.

Rejection under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1-16, 55, 66-72, 78-87 and 92-98 are rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Office Action

alleges that the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims, and that the claims are broader than the enablement provided by the disclosure with regard to all possible methods utilizing any co-crystal of or the atomic coordinates describing the three-dimensional structure of any fragment, variants or the full-length of PYK2 from any biological source. Applicants respectfully disagree with this rejection. As discussed above, the invention is directed to various methods of using some aspect of PYK2 and binding compound co-crystals, either the structure of the crystals, or an electronic representation thereof. The exemplary co-crystal and described methods of making such crystals should not limit the scope of these claims. One skilled in the art is fully enabled to use such co-crystal data to develop ligands according to Applicant's disclosure. Applicant's claims are directed to what is done with the information from the crystal once formed, which is fully enabled by the example provided. Applicants do not claim crystallization of any and all PYK2 with suitable compounds, rather, Applicants claim a method of using such crystals once they are formed. Applicants agree with the Office Action assessment that the molecular biological techniques and genetic manipulation to make any protein, general crystallization methods for proteins, and synthetic methods to make a compound that binds to PYK2 are known and the skill of the artisan is well developed (page 7, paragraph 2, lines 9-12). Such knowledge is sufficient to enable one skilled in the art to make and use co-crystals in addition to the one exemplified in Applicant's disclosure, and to practice Applicant's method of ligand development from the information resulting from the co-crystal. Applicant's example of a PYK2 co-crystal shows that such crystals are possible. It would be a matter of screening for crystallization conditions that could provide the desired crystal, where such screening is routine in the art of crystallography.

The Office Action also alleges on page 7, second paragraph

> While molecular biological techniques and genetic manipulation to make any protein, a general crystallization methods for proteins, and synthetic method to make any compound that binds to PYK2 are known in the prior art and the skill of the artisan are well developed, knowledge regarding crystallization of a particular protein and its complexes is lacking. It is well established in the art that obtaining a protein and its complexes in a

> crystal form is highly unpredictable without any clear expectation of success...the skilled artesian [sic] would be expected to screen large number of crystallization conditions...A protein which may crystallize under specific crystallization condition, it [sic] mutants may or may not crystallize under the same condition.

Applicants believe that this argument is irrelevant to practicing Applicant's claimed invention. The invention is not directed to taking a specific PYK2 polypeptide and compound and making a crystal, but in taking the data from any co-crystal and using the data according to the claimed invention. It would be expected of one skilled in the art to take any PYK2 polypeptide and compound and screen many conditions in the hope of finding the condition that provides a suitable co-crystal, or to continue screening additional PYK2 polypeptides until an appropriate crystal is found. It is because of the unpredictability in the art that such extensive screening may be required. This is not, however, undue experimentation in the art of crystallography, but is recognized to be necessary, but routine experimentation in order to find appropriate conditions for crystals, if such conditions can be found. Applicants' claimed method can readily be carried out with any crystal which meets the parameters set forth herein, once such crystal has been obtained. The present claims, therefore, should not be limited by the single co-crystal example provided.

Further, the Office Action on page 8, lines 4-10, suggests

> ...searching for a crystallization conditions [sic] for a protein and its complexes that is suitable for X-ray crystallography and determining its three-dimensional structure by the X-ray diffraction method is well outside the realm of routine experimentation and predictability in the art of success is extremely low. The amount of experimentation to identify a crystal for a PYK2 polypeptide or any mutant, fragment, or co-crystal thereof suitable structure determination by the X-ray crystallography method and determine the structure is enormous .

Again, Applicants disagree with this assessment of the art. While the rate of successful crystallization may be low, i.e. many conditions and/or polypeptides may need to be screened to provide few crystals, this large amount of experimentation is not undue as it may be necessary in order to find a condition that provides crystals. That such a large amount of experimentation may be required does not make it outside the realm of routine experimentation, rather, this large

amount of screening with a low success rate is routine in the art of crystallography. Applicants have shown that such crystals can be formed successfully; based on Applicants' success, one skilled in the art, with experimentation considered routine in the art of crystallography, would attempt to find at least one condition out of many that results in a suitable co-crystal. Applicants reiterate that the claims are not directed to forming the crystals, only to what is done with the information obtained from the crystals. Such crystals are provided by routine, albeit potentially extensive, experimentation, that is simply the expectation of those of skill in the field of crystallography.

While Applicants believe the claims as amended are fully enabled, new claims 99-104 have been added to define the invention with greater particularity. Claim 99 includes the step of using a crystallization screening kit to identify crystallization conditions for forming the co-crystals of claim 1, with claim 100 adding the step of determining the structure by X-ray crystallography. Claim 101 includes the step of forming the co-crystal of claim 1 under specific conditions, with claim 102 adding the step of determining the structure by X-ray crystallography. Claim 103 includes the step of forming the co-crystal of claim 1 using PYK2 kinase domain that contains a portion of at least 50 amino acid residues with greater than 90% identity to at least a portion of SEQ ID NO: 1, with claim 100 adding the step of determining the structure by X-ray crystallography.

Applicants believe that based on amendments to the claims and the arguments presented herein, the claims are enabled. Applicants respectfully request withdrawal of the 35 U.S.C. 112, first paragraph enablement rejection.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 1-16, 55, 66-72, 78-87 and 92-98 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, as follows:

(a) Claim 1 is allegedly incomplete for omitting essential method steps, where the allegedly omitted steps are indicated as (a) co-crystallization of PYK2 of SEQ ID NO: 1...; (b) determine the three dimensional structure by the X-ray diffraction method; (c) determine the arrangement of said compound bound to the binding site; (d) modify the compound; and (e) test the modified compound ability to modulate the activity of PYK2 (see page 8, lines 31-38 of the Office Action). Applicants respectfully disagree that these are required steps. The method involves using the information from the co-crystal, where the co-crystal and information are provided by methods known in the art, as exemplified by the specification (e.g. forming a co-crystal with PYK2 of SEQ ID NO: 1 and using X-ray crystallography). The method may be practiced from any available information from a co-crystal, the co-crystallization and structure determination are not essential to the method. Applicants point out that suggested step (c) is already provided in the claim, i.e. determining the orientation of at least one compound bound with PYK2 in a co-crystal. In order to further prosecution, Applicants have amended claim 1 without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. Amended claim 1 includes the steps of modifying a chemical structure of the compound and testing for activity with PYK2, consistent with suggested steps (d) and (e).

(b) The phrase "binds weakly" in claims 2 and 16 is allegedly a relative term, which allegedly renders the claim indefinite. While Applicants respectfully disagree, in order to reduce the issues and expedite prosecution, Applicants have amended these claims, replacing the phrase "binds weakly" with the phrase "binds with low or very low affinity," where binding with low or very low affinity is clearly defined in the specification.

(c) Claim 7 is allegedly incomplete as the formula is undefined and it does not end in a period. The claim has been amended to include Formula I, and a period is added.

(d) Claim 8 is allegedly incomplete for omitting essential method steps, where the step of how to identify a compound that binds to PYK2 is allegedly omitted. Applicants respectfully disagree, the method includes the step of identifying the compounds, how the

compound is identified is not essential to the claim, as one of skill in the art is well aware of numerous methods by which the compound could be identified.

(e) Claims 12 and 15 are allegedly incomplete for omitting essential method steps. In order to further prosecution, Applicants have amended claims 12 and 15 without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. The amended claims include the step of modifying a chemical structure of the compound to provide a derivative.

(f) Claim 66 as a whole is allegedly incomplete. The phrases "a biological agent" and "one sub-structure" are allegedly indefinite terms. Applicants have amended claim 66 to include a Markush group of possible sub-structures as well as a Markush group of possible biological agents.

(g) Claim 78 recites the limitation "the method of claim 82...". The reference to 82 is an inadvertent typographical error, and should have been reference to claim 72. The claim has been amended accordingly.

(h) The method of claim 92 is allegedly confusing and considered indefinite. In order to further prosecution, Applicants have amended claim 92 without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. The amended claim includes the steps of creating a homology model and including a compound of Formula I in the binding site of the homology model.

(i) The phrase "energetically allowed sites" in claim 79 allegedly renders the claim indefinite. Applicants are not entirely clear as to the argument that the term is indefinite, as the Office Action suggests in one sentence that there are absolute standards in the art for ascertaining the energy allowed sites, and in the next sentence, suggests that it is a relative term subject to interpretation of individuals. However, in efforts to reduce the issues and expedite prosecution,

Applicants have amended the claim to indicate that the energetically allowed sites are on the PYK2 binding compound.

(j) Claims 3-6, 9-15, 67-71, 80-87, and 93-98 are included with these rejections because they are dependent on rejected claims and do not cure its deficiencies. Applicants believe that based on the amendments to claims and arguments presented herein, these claims are dependent on valid claims.

Based on the amendments to the claims and arguments presented, Applicants respectfully request that all 35 U.S.C. 112, second paragraph rejections be withdrawn.

Rejection under 35 U.S.C. § 103(a)

Claims 8-16, 55, 66-72, 78-87 and 92-98 are rejected under 35 U.S.C. 103(a) as allegedly being unpatentable over the commercial availability of computers and various software packages the structure of a candidate compound to the structure of a protein such as PYK2 [sic], see for example U.S. patent 6,197,495 ('495), in view of U.S. patents 5,837,524 ('524) and U.S. patent 6,100,254 ('254). The Office Action alleges that the '495 exemplifies the state of the prior art of identifying molecules that bind with a target protein based on three-dimensional structure, that the '495 [sic, Applicants believe this should be '524] teaches human PYK2 amino and nucleic acid sequences and method of expression, as well as methods of identifying compounds that bind PYK2, and that the '254 teaches inhibitors of protein tyrosine kinases including compounds that fit formula I of the instant application. Applicants respectfully disagree with the rejection.

Further, the Office Action suggests the following:

> The '245 [sic, Applicants believe this should be '524] patent provides one of ordinary skill in the art with motivation to identify potential inhibitor for SYK2 [sic] as they teach that inhibitors of SYK2 [sic] can be used for the treatment of stroke, Alzheimer's...Thus, it would have been obvious to one of ordinary skill in the art to use a commercially available computer equipped with software packages...among others taught in the '495 patent to fit a model structure of a potential inhibitor to the three-dimensional structure of SYK2 [sic] to identify possible inhibitors for SYK2 [sic] activity...The only difference

> between the cited prior art above and the claimed invention are the atomic coordinates in the application...Atomic coordinate can't render a known method for identifying inhibitors of SYK2 [sic] of claims 8-11. The ordinary skill in the art would have the choice of many compounds known to inhibit protein kinases in general and tyrosine kinases, in particular such as those triazol derivatives of 1,4-benzodiazopine-2-one taught in the '254 patent to screen for highly selective inhibitor of SYK2 [sic]...It would have been further obvious to the ordinary skilled artisan to synthesize the potential inhibitor and contacting it with SYK2 [sic] to identify its specificity and selectivity for SYK2 [sic] (claim 55). Since aberrant SYK2 [sic] activity is associated with neurodegenerative diseases, one of ordinary skill in the art would have been further motivated to identify a surface loop in SYK2 or at least 6 amino acid residues on the protein surface, which can be used as an antigen and use it to raise specific antibody to use for diagnostic purposes. Thus, the ordinary the skill in the art [sic] would display the structure of the protein on a computer screen and visually identify potential antigen (claims 66, 67, 69-71). Also, algorithms to identifying mutant with altered desired characteristic are well known in the prior art (claim 68 [sic, Applicants believe this should be 66]).

While Applicants respectfully disagree with the assertions set forth above, in order to further prosecution, Applicants have amended independent claims 8, 12, 55, 66, 72, 79, and 92, without prejudice, and reserve the right to pursue claims as originally filed in a continuation application. Concerning claims 8 and 12, these involve the steps of identifying binding compounds, modifying the compounds to provide a derivative, and assessing the binding of the resulting derivative. There is no teaching of these steps in the '495, which essentially screens compounds for binding to a protein, which would amount to the step of identifying binding compounds. There is no teaching of modifying such a binding compound to provide a derivative, nor of assessing the activity of this derivative. Neither the '524 nor the '254 patents provide these steps, as such there is no teaching of Applicant's claims in the combination of references cited.

Similarly, claim 55 includes the step of modifying a compound to provide a derivative, then determining the activity of the derivative with respect to PYK2, which, as discussed above, is not taught by any combination of the references cited. Further, the derivative contemplated by the claim has a core structure of Formula I, which would not be obvious based on the '254. While the '254 patent teaches a broad range of compounds, the reference provides no direction to select compounds with a triazole R group, even though there are many possible R groups to

select from in the '254. While the '254 patent is generally directed to tyrosine kinase inhibitors, there is no mention therein of PYK2 specifically. Therefore, since there are many tyrosine kinases known in the art, but the '254 patent does not specifically mention PYK2, there can be no suggestion in the art to develop inhibitors of PYK2, a tyrosine kinase that is not even specifically mentioned in the '254.

Regarding claim 66, Applicants respectfully disagree with the arguments presented that one of skill in the art would be motivated to identify a surface loop in PYK2 which can be used as an antigen to raise antibody based on aberrant activity associated with neurodegenerative diseases. It is not at all clear from the argument presented how activity associated with neurodegenerative disease leads to motivation to produce antibody. Further, there would be no motivation to display the structure of the protein on a computer and visually identify potential antigen, nor to identify mutant with altered characteristics, other than improper hindsight motivation having benefit of Applicant's disclosure. As such, there is no teaching in any combination of the cited references to identify a sub-structure and form a biological agent from the sub-structure.

Regarding claims 72 and 92, these claims as currently amended include a compound of Formula I, either fitting such compound in an electronic representation (claim 72) or including such compound in the binding site of a homology model. As discussed above, there is no teaching based on the '254 patent to select such compounds of Formula I in the development of PYK2 binding compounds.

Regarding claim 79, this is directed to identifying an allowed site on PYK2 for attachment of an attachment component and attaching such component to the PYK2 binding compound. None of the references cited, nor any combination thereof, teach the attachment of an attachment component to PYK2 binding compounds.

Based on the claim amendments and arguments presented herein, Applicants believe that the claims are not obvious based on any combination of the cited references. Applicants respectfully request withdrawal of the 35 U.S.C. 103(a) rejection.

Conclusion

In view of the above amendments and remarks, prompt and favorable action are respectfully requested. In the event that any matters remain to be resolved in view of this communication, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

With the petition for extension of time provided herewith, this submission is filed timely. No additional fee is believed due with the present submission. However, the Commissioner is hereby authorized to charge any additional fees which may be required regarding this application, or credit any overpayment, to Deposit Account No. 50-0872.

Respectfully submitted,

Date October 23, 2006

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